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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/564,945	01/09/2007	Katherine Weilbaecher	60005161-0217	4085

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EXAMINER	
RAO, SAVITHA M	
ART UNIT	PAPER NUMBER
1614	

MAIL DATE	DELIVERY MODE
03/16/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/564,945	WEILBAECHER ET AL.	
	Examiner	Art Unit	
	SAVITHA RAO	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *02 January 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16,18-21 and 23-42* is/are pending in the application.

4a) Of the above claim(s) *1-12 and 25-42* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-16 and 18-21 and 23-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-16, 18-21 and 23-42 are pending and are subject of this office action.

Receipt and consideration of Applicants' amended claim set and remarks/arguments mailed on January 2nd 2009 is acknowledged. Claims 1-12 and 25-42 are withdrawn as being drawn to a non-elected invention. Claims 13-16 and 18-21 and 23-24 are under consideration in the instant office action

Applicants' arguments, filed 01/02/2009, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Rejection of Claims 13-14, 18-21 and 23-24 under 35 U.S.C. 103(a) as being unpatentable Fisher et al (US 6291469, referenced in the instant IDS) in view of Pitts et al (US 6489333) further in view of Trikha et al (Cancer Research, vol. 57, pp 2522-2528 (1997)) **is maintained** for reasons of record restated below.

Examiner finds applicants argument to the claim interpretation of instant claims 15-16 and thereby will rejoin them with the present set of claims. The subject matter of instant claims 15-16 is properly rejected under the following rejection since the amended claims 15 and 16 is drawn to the method of inhibiting the tumor cell where in the tumor cell is contained within a bone of the skeletal system of the subject.

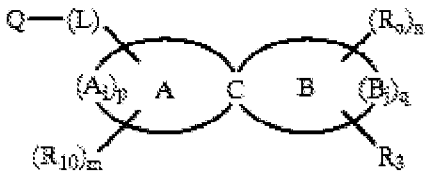
The rejection below provides an ordinary skilled artisan to use spiro compounds similar to those taught by Fisher et al in the treatment of metastatic melanoma cells by virtue of their ability to block GpIIb/IIIa ($\alpha IIb\beta 3$ integrin receptors) which are present on melanoma cells as taught by Trikha et al. Since the compounds act by binding to the receptor on the cancer cells, they prevent cell-cell adhesion and thereby inhibit tumor cell growth. Irrespective of the organ system in the subject the activity of the compounds on the tumor cell would be consistent and thereby an ordinary skilled artisan would

develop such a method to inhibit tumor cell growth in the bone of the skeletal system of the subject with a reasonable expectation of success that such a treatment would indeed generate in decreased tumor cell growth.

Previous rejection:

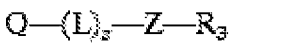
Fisher teaches novel spiro compounds that block the GPIIb/IIIa fibrinogen receptor (same as αIIbβ3 receptors as evidenced by Pitts and Trikha et al. secondary references used in this rejection), thereby inhibiting platelet aggregation and subsequent thrombus formation (col1, lines 40-43).

Fisher teaches certain spirocyclic compounds having a spiro nucleus formed form two fused rings A and B represented by the formula (I) below and all pharmaceutically acceptable salts, solvates and prodrug derivatives thereof (abstract and col.1, liens 49-61)



(I)

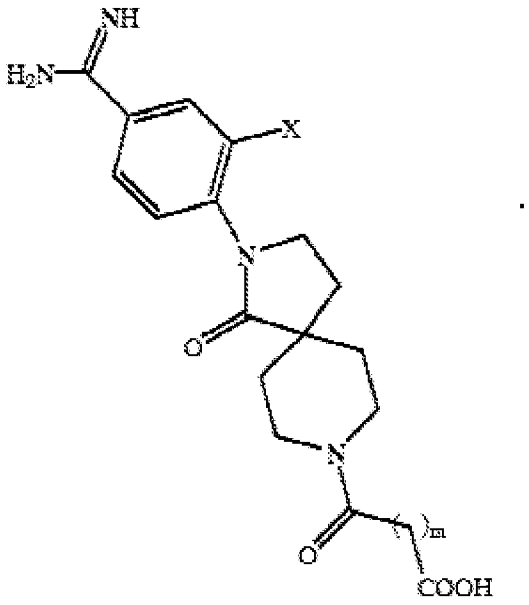
Fisher teaches compounds of formula (II) below



(II)

wherein Z is a spirocyclic nuclease selected from (A) (B) (C) or (D) described in col.4, lines 35 to col. 5, lines 10.

Fisher teaches among one of the most preferred subset of compounds the following compound (col. 39, lines 49-65) where X is F or H, m is 0-4 (col.31, line 1)



Fisher teaches prodrugs of the compounds of his inventions which have metabolically cleavable groups and become by solvolysis or under physiological conditions the compounds of the inventions which are pharmaceutically active in vivo, for e.g., ester derivatives of the compounds are often active in vivo, but not in vitro (col. 43, lines 47-52). Fisher further teaches that simple aliphatic and aromatic esters derived from acidic groups, pendant on the compounds of his invention are preferred prodrugs (col. 43, lines 62-64). Finally Fisher teaches a method of preventing or treating thrombosis in mammals, especially humans, with therapeutically effective amount of the compound of his invention, indications of which includes arteriosclerosis, acute ischemic

attacks and strokes, peripheral vascular disease, etc. (col.166, lines 40-56) and teaches other indications wherein the platelet aggregation inhibitors of his inventions have potential use for (col.167, lines 1-21).

Fisher is silent as to the use of the compounds with Spiro nucleus that inhibit αIIbβ3 receptors in a method of preventing or inhibiting tumor cell growth in a subject.

However, Pitts et. al. teaches novel heterocycles which are useful as antagonists of the αvβ3 and αIIbβ3 integrin and related cell surface adhesive protein receptors and methods of using the compounds for the inhibition of cell adhesion, treatment of antigenic disorders, inflammation, bone degradation, cancer metastasis and other condition mediated by cell adhesion and/or cell migration and/or angiogenesis (abstract) Pitts teaches that Tumor dissemination, or metastasis, involves several distinct and complementary components, including the penetration and transversion of tumor cells through basement membranes and the establishment of self-sustaining tumor foci in diverse organ systems To this end, the development and proliferation of new blood vessels, or angiogenesis, is critical to tumor survival. Without neovascularization, tumor cells lack the nourishment to divide and will not be able to leave the primary tumor site (col.1, lines 36-44).Pits additionally teaches that inhibition of angiogenesis in animal models of cancer has been shown to result in tumor growth suppression and prevention of metastatic growth and many angiogenic inhibitors have been directed toward blocking initial cytokine-dependent induction of new vessel growth, e.g. antibodies to endothelial cell growth factors. Pitts also teaches that a general approach which would allow for inhibition of angiogenesis due to a variety of stimuli wound be of benefit (col.1,

lines 46-55). Pitts teaches that, since several endogenous agonists are involved in activating platelet function and aggregation, an inhibitor which acts against all agonist would represent a more efficacious antiplatelet agent than currently available anti-platelet drugs which are agonist specific (col.3, lines 25-37) . Pitts additionally teaches a common pathway for all known agonists namely platelet glycoprotein IIb/IIa complex (GpIIb/IIIa), a membrane protein mediating platelet aggregation which is a member of integrin family also referred to as fibrinogen receptor or the αIIbβ3 integrin (col.3, lines 46-51). Compounds taught by Pitts binds to integrin receptors thereby altering cell-matrix and cell-cell adhesion processes and are useful for the inhibition of cell adhesion and the treatment of cancer metastases among other indications. (col.4, lines 61-67).

Pitts does not teach αIIbβ3 antagonists being used for inhibition of tumor cell growth specifically melanoma cells growth.

However, Trikha teaches fibronectin-adherant melanoma cells possess an intracellularly localized pool of high-affinity αIIbβ3 receptors (abstract). Trikha teaches that integrins are cell surface receptors (αIIbβ3 and αvβ3) which mediate homotypic and heterotypic interactions among tumor cells and host cells in addition to tumor cell interactions with tumor cell-extracellular matrix (ECM) (page 2522, left col., 1st paragraph). Trikha teaches that the integrin αIIbβ3, originally termed as GPIIb-IIIa was initially identified in platelets and is directly involved in platelet aggregation and cell signaling and ligand binding to αIIbβ3 alters the state of intracellular kinases, GTPases and phospholipases (page 2522, right col. 2nd paragraph). Trikha also teaches that

B16a murine melanoma cells expresses the αIIbβ3 integrin and that this receptor plays an important role in tumor cell-platelet, tumor cell-endothelial cell and tumor cell-ECM interactions (page 2522, right col. 3rd paragraph). Trikha demonstrates detection and expression of αIIbβ3 in three human melanoma WM 983B, WM 983A and WM 35 cell lines through several different *in-vitro* experimental procedures (page 2524 right col. 2nd paragraph) and demonstrated expression of αIIbβ3 in melanoma tumors [skin melanoma specimens form two Hungarian woman aged 27 and 35 (page 2524, left col. 2nd paragraph)] through *in-vivo* studies (page 2526, left col. 2nd paragraph) and concludes that αIIbβ3 can be detected in melanoma tumor *in-vivo* and cultured melanoma cells *in-vitro* and is capable of directly supporting melanoma cell adhesion as is involved in invasion (page 2527, right col. last paragraph).

In view of the foregoing references, the instantly claimed method for of inhibiting tumor cell growth with αIIbβ3 inhibitors such as the instantly claimed spiro compounds would have been prima facia obvious to one of ordinary skill in the art at the time the invention was made. Fisher discloses spiro compounds identical to the generic compounds claimed in instant claim 20 and 21 and compounds structurally similar to the instantly elected specie including the ester prodrug. Fisher additionally teaches the spiro compounds to be platelet-specific activated αIIbβ3 receptor antagonists which inhibits platelet aggregation and thrombus formation. Pitts teaches use of compounds which are integrin receptors antagonists for inhibition of cell adhesion and the treatment of cancer metastases among other indications. Finally, Trikha demonstrates expression of αIIbβ3 receptors both in-vitro in melanoma cells and in-vivo in melanoma tumor samples.

Accordingly, an ordinarily skilled artisan would be motivated to use structurally similar compounds taught in the prior art to be αIIbβ3 receptor antagonists that inhibits platelet aggregation, in a method to inhibit melanoma tumor growth. Pitts also teaches solutions to the problem of using a agonist specific anti-platelet inhibitor in treatment procedures which is to a general approach which would allow for inhibition of angiogenesis due to a variety of stimuli such as using integrin receptor antagonists which alter cell-matrix and cell-cell adhesion processes and are useful for the inhibition of cell adhesion and the treatment of cancer metastases. This solutions to the prior art problem also provides the skilled artisan motivation to combine the references. An ordinarily skilled artisan will be imbued with at least a reasonable expectation of success that a method of treating melanoma tumors with spiro compounds that inhibit platelet aggregation will result in decrease in tumor growth and prevention of invasion.

Response to applicant's arguments filed on 01/02/2009:

Applicant traverses the above rejection with the following arguments: a. The PTO does not establish that the cited references provide a reasonable expectation of success.

Applicant's traversal arguments for this rejection have been fully considered, but are not found to be persuasive.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., "bone microenvironment unable to support tumor cell growth") are not recited in the

rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

As such absence of such a teaching in the references used does not prevent an ordinarily skilled artisan to be imbued with a reasonable expectation of success. An expectation of success in this instance is provided by the prior teachings of the following: a) Fisher's teaching that spiro compounds similar to the instantly claimed compounds block platelet membrane glycoprotein complex GpIIb/IIa (fibrinogen receptor) thus resulting in inhibition of platelet aggregation and therefore useful in treatment of thrombogenic diseases. b) Pitts teaching that platelet glycoprotein IIb/IIa complex (GpIIb/IIa) is a member of the integrin family which is also referred to as αIIbβ3 integrin and inhibitors of this receptors have been shown to alter cell matrix and cell-cell adhesion process and are useful for the inhibition of cell adhesion and the treatment of cancer metastasis. c) Trikha's teachings that fibronectin-melanoma cells possess intracellularly localized pool of high-affinity αIIbβ3 integrin receptors which mediate homotypic and heterotypic interactions among tumor cells and host cells in addition to tumor cell interaction with tumor cell-extracellular matrix.

The fact pattern set forth by the teachings of the three references clearly provides motivation to one of ordinary skill in the art to use compounds which inhibit GpII/IIIa complex (αIIbβ3 integrin or fibrinogen receptor) in a method of inhibiting melanoma tumor growth. As such an ordinarily skilled artisan would be imbued with a reasonable expectation of success that such a compound would bind to the similar

receptors available on melanoma cells and act by preventing cell-cell adhesion or tumor-cell extracellular matrix interaction.

Examiner disagrees with the examiner's argument that platelet aggregation is a phenomenon that occurs apart from the bone microenvironment and thereby not indicative of use in treating bone metastasis of melanoma cells. The clinical correlation between platelet dysfunction and cancer progression is supported by the finding that platelets have an essential role in numerous models of experimental metastasis. Depletion of platelets by a variety of mechanisms reduce the number of metastases to lung and bone. Integrilin a pharmacological αIIbβ3 integrin antagonist and inhibitor of platelet aggregation has been shown to provide significant reduction in osteolytic bone metastasis formation. As such the prior art references used in this rejection provides one of ordinary skill in the art a reasonable expectation of success that a method of inhibiting tumor cell growth in a subject by administering spiro compounds as taught by Fisher would result in a potentially useful therapeutic option for treating tumors and prevent metastasis. It is to be noted that In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

Conclusion

Claims 1-16, 18-21 and 23-42 are rejected. No claims are allowed

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAVITHA RAO whose telephone number is (571)270-5315. The examiner can normally be reached on Mon-Fri 7.00 am to 4.00 pm..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SAVITHA RAO/

Examiner, Art Unit 1614

/Ardin Marschel/

Supervisory Patent Examiner, Art Unit 1614